REMARKS

Claims 43, 58, 60, 61 and 69-74 constitute the pending claims in the present application, prior to Amendment. Applicants cancel, without prejudice, claims 43, 58, 60, 61, and 69. Cancellation of these claims is solely to expedite prosecution and is not in acquiescence to any of the rejections raised in this or prior office actions. Applicants expressly reserve the right to prosecute claims of similar or differing scope in future applications.

Applicants add new claim 75. Support for Applicants' amendment can be found, for example, in paragraph [0042] of the published specification. No new matter has been entered. New claim 75 reads on the elected invention and species.

Continued Examination under 37 CFR § 1.114

Applicants note that the finality of the previous Office Action has been withdrawn in view of Applicants' Request for Continued Examination received June 25, 2008.

Status of Application, Amendments, and/or Claims

Applicants note with appreciation that Applicants' June 25, 2008 amendment has been entered in full.

The Examiner has withdrawn claims 61, 73 and 74 from further consideration pursuant to 37 C.F.R. 1.142(b) as allegedly drawn to a nonelected species.

Applicants have substituted the status identifier associated with claim 73 to recite "Withdrawn".

Applicants respectfully traverse the Examiner's argument with respect to claim 74 being drawn to a nonelected species. A hemangioma is a solid, albeit benign, tumor and therefore is drawn to the elected species of solid tumors. However, for the purpose of clarity, applicants have amended claim 74 such that it depends from claim 71. Applicants' amendment is believed to clarify Applicants' position that claim 74 is directed to an elected species.

Issues Raised in the Office Action Mailed October 9, 2008

Information Disclosure Statement

Applicants note with appreciation that the Information Disclosure Statement received June 25, 2008 has been considered.

Withdrawn Objections and/or Rejections

Applicants note that the rejection to claims 43, 58 and 60 under 35 U.S.C. § 112, first paragraph, for allegedly failing to comply with the written description requirement is withdrawn in view of Applicants' amendments to the claims.

Applicants also note that the rejection to claims 43 and 58 under 35 U.S.C. § 112, first paragraph, for allegedly containing new matter is withdrawn in view of Applicants' amendments to the claims.

Claim Rejection – 35 U.S.C. § 112, first paragraph, enablement

Claims 43, 58, 60 and 69-72 are rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. Applicants traverse this rejection.

As an initial point, and as detailed above, Applicants have cancelled, without prejudice, claims 43, 58, 60 and 69. Cancellation of claims 43, 58, 60, and 69 is solely to expedite prosecution and is not in acquiescence to any of the rejections raised in this or prior Office Actions. Cancellation of claims 43, 58, 60, and 69 renders their rejection moot.

Below, Applicants provide detailed arguments and evidence to further support the conclusion that claims 70-72 and 74 are enabled throughout their scope.[1]

A. Claims 43, 58 and 70 Are Not Overly Broad With Respect to the Encompassed Conditions Related to Vascular Growth

The Examiner argues that claims 43, 58 and 70 are extremely broad with respect to the encompassed conditions related to vascular growth. Specifically, the Examiner contends that the claims allegedly encompass treatment of diseases associated with enhanced vascular growth wherein inhibition of angiogenesis is contrary to treatment of the disease. As support for the Examiner's argument, the Examiner contends that inhibition of the angiogenesis that occurs in ischemia would be a harmful or unproductive treatment of that condition.

Applicants contend that it would have been clear to the skilled artisan to administer a Shh-blocking antibody only in those cases where inhibition of angiogenesis would be beneficial

[1] Applicants further contend that withdrawn claim 73 is fully enabled by the specification.

in treating a disease. However, solely to advance prosecution, applicants have canceled claim 43 and dependent claim 58. As detailed above, cancellation of these claims is solely to expedite prosecution. Applicants expressly reserve the right to prosecute claims of similar or differing scope.

In the context of claim 70, Applicants respectfully traverse the Examiner's arguments. Applicants contend that the scope of claim 70 is clear and refers with particularity to a certain class of conditions for which inhibition of vascular growth is therapeutically efficacious. Support for claim 70 can be found within paragraph [0118] of the pending application. Paragraph [0118] states that the invention can be used for "inhibiting vascular growth in subjects suffering from excess vascularization or neovascularization as found in, for example, a variety of solid tumors such as breast cancer, hemangiomas in infancy, ocular neovascularization associated with diabetes, bleeding disorders of the female reproductive tract, and certain forms of arthritis". In all of the diseases or conditions described in this paragraph, inhibition of excess vascularization or neovascularization would be expected to result in disease amelioration. Therefore, treatment of these diseases by administering a Shh blocking antibody to inhibit vascular growth is therapeutically indicated and beneficial. Claim 70 does not encompass conditions such as ischemia in which inhibition of vascular growth may be counter-indicated.

In view of the clear guidance provided by the specification, as well as the level of skill in the art, Applicants submit that claim 70 is fully enabled. Reconsideration and withdrawal of this aspect of the rejection is requested.

B. The Specification as Filed Provides Sufficient Guidance to the Skilled Artisan with Respect to Practicing the Claimed Method

The Examiner argues that the specification provides minimal guidance to the skilled artisan with respect to practicing the claimed method on solid tumors. In addition, the Examiner contends that the specification does not provide any *in vivo* working examples of treatment of a condition of "abnormally enhanced vascular growth" with a "Sonic hedgehog blocking antibody". Applicants respectfully traverse.

Applicants' specification provides a working example, Example 4, that illustrates that a Shh blocking antibody inhibits vascular growth and erythropoiesis in whole mouse embryonic cultures. Applicants contend that, by teaching that a Shh blocking antibody could be used for the

purposes of inhibiting vascular growth, they have therefore provided sufficient guidance to the skilled artisan with respect to practicing the claimed method. Applicants note that satisfaction of the enablement requirement does not turn on the presence or absence of working examples. See, *e.g.*, MPEP 2164.02.

As previously discussed in the Response received June 25, 2008, it was well understood by the skilled artisan at the effective filing date, as it is well understood by the skilled artisan today, that inhibition of the blood supply feeding a tumor could be used as a treatment for cancer. Applicants maintain their arguments, as put forth in the previously filed Response, that the claimed method does not rely on targeting tumor cells *per se*. Rather, the claimed method targets the vascular growth that accompanies the tumor, thereby making the claimed method beneficial across a range of tumors of diverse etiology. As it was known in the art as of the effective filing date of the instant application that inhibition of vascular growth was a beneficial treatment for tumors, Applicants' specification need not provide a detailed description of this information. See, *e.g.*, MPEP § 2163(II)(A)(2).

The Examiner also argues that the specification does not provide any *in vitro* models that correlate with *in vivo* treatment. As discussed above and in the previously filed Response, Applicants are not required to provide working examples demonstrating *in vivo* treatment using the claimed method. The value and utility of inhibiting vascular growth for the purpose of treating solid tumors was amply appreciated by the skilled artisan as of the effective filing date of the instant application. In addition, while a mouse embryonic culture is not typically classified as being an *in vivo* model, embryonic cultures were described at the filing date as being useful systems for studying the processes of erythropoiesis and vasculogenesis. See, *e.g.*, final paragraph on page 162 of Palis et al., 1995. 86(1):156-63, a copy of which is included as Exhibit 1.

Accordingly, Applicants contend that the specification as originally filed provides sufficient guidance to the skilled artisan with respect to practicing the claimed method. In addition, although Applicants contend that the specification **does** provide a working example in support of the presently claimed invention, Applicants note that compliance with the enablement requirement does not hinge on the provision of *in vivo* working examples in the specification. When, as in the instant case, there is a well understood connection between inhibition of vascular growth and, for example, therapeutic treatment of tumors, an actual *in vivo* example is not

required to enable the practice of the claimed invention. Reconsideration and withdrawal of this aspect of the rejection is requested.

C. Examples 3-6 Support the Scope of the Claimed Invention

The Examiner alleges that Examples 3-6 of the specification provide teachings that are very limited in relation to the claimed inventions. Specifically, the Examiner argues that these examples in the specification are all allegedly related to *in vitro* hematopoiesis rather than vascular growth, and that hematopoiesis is a different molecular process from vascular growth.

As acknowledged by the Examiner, Examples 3-6 utilized ϵ-globin as a marker of erythroid cell formation. The peptide ϵ-globin is a subunit of embryonic hemoglobin. While the Examiner is correct in noting that ϵ-globin levels can be used to assess hematopoiesis, the pending application also teaches that ϵ-globin can be used to assess vascular growth. In paragraph [0015] of the pending application, Applicants taught the use of a transgenic mouse that is capable of expressing ϵ-globin for a prolonged period and then evaluating the effects of a compound on the stimulation of hematopoiesis *and* vascular growth by measuring ϵ-globin. In addition, paragraph [0089] summarizes the results from several experiments (Example 3-5) in which the role of Shh in hematopoiesis and vasculogenesis was examined. In all of these experiments, ϵ-globin was used as a marker for *both* hematopoiesis and vasculogenesis. See paragraph [0090] of the pending application, which states that "[t]he above assays show that hedgehog proteins expressed in extraembryonic tissue as well as hedgehog proteins that are closely related to proteins expressed in extraembryonic tissues, stimulate hematopoiesis and vasculogenesis". Therefore, it is clear from the application as filed that ϵ-globin may serve as a marker of both hematopoiesis and vasculogenesis.

Furthermore, hemoglobin, which is comprised of the ϵ-globin subunit in embryonic tissue, was, and still is, a commonly used marker for both angiogenesis and vasculogenesis. See, *e.g.*, Robertson et al., 1991, Cancer Research, 51:1339-44; Hu et al., 1993. Br.J.Pharmacol. 109:14-17; Teunis et al., 2002, Faseb Journal, 16: 1465-67; Yoshida et al., 2003, Laboratory Investigation, 83(10):1385-1394; Fang et al., 2007, Carcinogenesis, 28(4):858-64. Copies of these references are included as Exhibits 2-6.). Therefore hemoglobin, which in some instances includes the subunit ϵ-globin, was, and still is, a marker routinely used by researchers when evaluating levels of angiogenesis and vasculogenesis.

Therefore, contrary to the Examiner's arguments, Examples 3-6 are related to both hematopoiesis *and* vascular growth, as ϵ-globin may be used as a marker for either process. Reconsideration and withdrawal of this aspect of the rejection is requested.

D. The Pending Claims Are Enabled For the Treatment of Solid Tumors Using a Shh Blocking Antibody

The Examiner agrees that the post-filing date art supports a role for the hedgehog pathway in tumor growth and vascular growth associated with a certain subset of solid tumors. However, the Examiner alleges that the post-filing date art demonstrates that many solid tumors are not characterized by dysfunctions that lead to Shh overexpression. Specifically, the Examiner contends that the art allegedly provides evidence that many tumors of different tissues are not characterized by activation of the hedgehog signaling pathway such that Shh is overexpressed.

Applicants' maintain their argument, as previously put forth in the June 25, 2008 Response, that the claimed invention is not based on necessarily modulating hedgehog signaling in tumor cells, but rather on inhibiting enhanced vascular growth, such as the vascular growth accompanying a solid tumor. The Examiner has rejected Applicant's argument, and in turn argues that administration of a Shh blocking antibody would not result in treatment of a solid tumor unless the tumor exhibits overexpression of the Sonic hedgehog protein. Applicants respectfully traverse.

While all tumors may not overexpress Shh, vascular growth is still a crucial process in the development of most malignant solid tumors. Without angiogenesis, a solid tumor would be limited in its overall growth capacity and likely would be unable to metastasize. As demonstrated in Applicants' previous response, this concept was well understood in the art prior to Applicants' effective filing date. Therefore, while Shh overexpression may not be observed in all tumors, angiogenesis, which itself can be inhibited using an antagonist of hedgehog signaling, is a necessary component for development and maintenance of malignant solid tumors. Accordingly, based on the teachings of the instant application, one of skill in the art would appreciate that blocking Shh signaling by administering a Shh blocking antibody would inhibit the angiogenesis or neovascularization that is observed in developing solid tumors – regardless of whether the tumor itself is characterized by misregulation in hedgehog signaling.

Example 4 of the pending application teaches that administration of a Shh blocking antibody prevented vasculogenesis. Although the references pointed to by the Examiner state that many solid tumors are not themselves characterized by Shh overexpression, none of these references address the subject matter presently claimed. The references do not examine angiogenesis associated with these tumors, and are thus silent on whether a Sonic hedgehog antagonist, such as a Sonic hedgehog blocking antibody, can be used to inhibit angiogenesis associated with those tumors. Accordingly, Applicants respectfully submit that the Examiner has not provided any evidence to undermine Applicants' contention that the claims are enabled throughout their scope because the references relied upon by the Examiner simply do not address the efficacy of a Sonic hedgehog antagonist for inhibiting tumor associated vascular growth. In the absence of any basis to question or counter the arguments and evidence put forth by Applicants, Applicants respectfully submit that the rejection cannot be maintained. In view of the instant application and detailed appreciation in the art regarding the role of angiogenesis in facilitating solid tumor growth and metastasis, the claims are enabled throughout their scope.

Applicants contend that the references relied upon by the Examiner simply do not address the subject matter presently claimed. However, Applicants do want to specifically address one of the references cited by the Examiner, U.S. Pre-Grant Application Publication 2004/0110663 ("the '663 publication"). The '663 publication describes an experiment involving the administration of the Shh blocking antibody 5E1 to a xenograft mouse model that was generated using the cancer cell line SW480 – a cell line that is not characterized by expression of Sonic hedgehog. The authors of the '663 publication conclude that the 5E1 antibody did not effectively inhibit the growth of the solid tumor. However, as detailed above, this experiment simply does not address the question of whether the Sonic hedgehog antibody inhibited vascular growth associated with the tumor. As such, the '663 publication does not undermine the enablement of the claimed invention.

First, the example provided in the '663 publication and relied on by the examiner only examines tumor volume, and does not examine a single readout for evaluating angiogenesis. As such, the '663 publication is silent as to whether the 5E1 antibody had an effect on angiogenesis.

A second explanation for the observed failure of 5E1 to reduce tumor volume in this particular experiment is related to the specific cell line, SW480, used in making the xenograft. SW480 cancer cells are considered in the art to be unique tumor cell lines that express relatively

low levels of the angiogenic-inducing factor VEGF (Ellis et al. 2000. The Oncologist. 5(Suppl 1): 11-15, a copy of which is included as Exhibit 7). Further, this line expresses a form of p53, a known inhibitor of angiogenesis, that has retained some of its normal activity (Rochette et al. 2005. J. Mol. Biol. 352(1):44-7, a copy of which is included as Exhibit 8). Therefore, the SW480 cell line may generate an idiosyncratic class of tumors that, in contrast to most solid tumors, are not largely driven by angiogenesis. These unique features of SW480 cells would be readily appreciated by one of skill in the art.

In view of the forgoing, Applicants contend that the references relied upon by the Examiner, including the cited example from the '663 publication, fail to undermine the patentability of the claimed invention. As such, there is no evidence of record to counter or undermine the arguments and evidence presented in support of Applicants' position that the claims are enabled throughout their scope. Reconsideration and withdrawal of this rejection are requested.

Related Applications

The following co-pending applications have already been brought to the Examiner's attention and made of record during prosecution of this application: application serial number 10/727,195; application serial number 09/883,848; application serial number 10/652,686; application serial number 09/977,864; and application serial number 10/652,298. Prosecution in the co-pending applications is on going and Applicants invite the Examiner to consider all prior, current, and future prosecution in the co-pending applications.

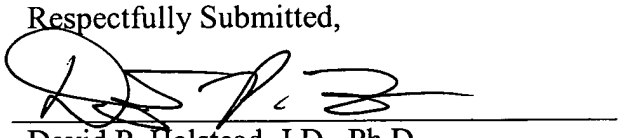
The most recent action in application serial number 10/727,195 is a reply dated January 21, 2009 (responsive to a non-final Office Action mailed September 28, 2008). The most recent action in application serial number 09/883,848 is a Notice of Appeal mailed September 4, 2008 (responsive to a final Office Action mailed March 3, 2008). Application serial number 10/652,686 issued March 3, 2009 as U.S. Patent No. 7,498,304. The most recent action in application serial number 09/977,864 is a final Office Action mailed March 3, 2009. The most recent action in application serial number 10/652,298 is a final Office Action mailed March 23, 2009.

CONCLUSION

If any clarification of the above response would facilitate prosecution of this application, Applicants respectfully request that the Examiner contact the undersigned at 617-951-7000. Should any further extension or other fee be required for timely consideration of this submission, Applicants hereby petition for same and request that the fee be charged to **Deposit Account No. 18-1945, under Order No. HUIP-P02-060**.

Respectfully Submitted,

Date: April 9, 2009



David P. Halstead, J.D., Ph.D.
Reg. No. 44,735
Ropes & Gray LLP
One International Place
Boston, MA 02110
Phone: 617-951-7000
Fax: 617-951-7050